Wyeth Perspective on Inhibitor Development

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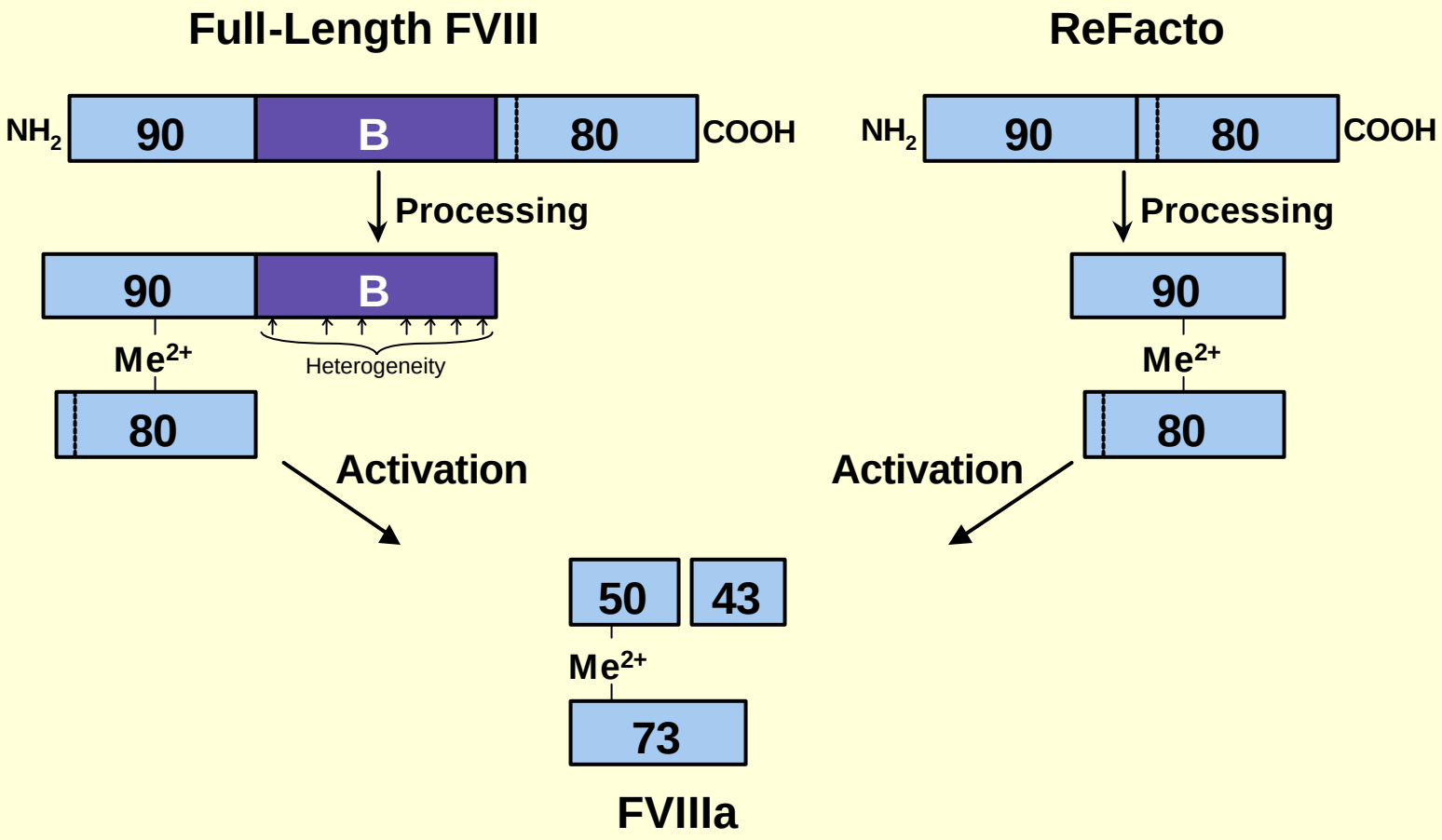
Inhibitors in Hemophilia A

- **Inhibitors are one of the most important safety concerns for all hemophilia patients**
  - rFVIII and pdFVIII have similar incidence of inhibitors in clinical trials
  - rFVIII and pdFVIII have low incidence of high-titer inhibitors in PTPs
  - Literature and registries support these findings
- **Establish uniform standards**
- **Global surveillance program should be implemented for all products**

ReFacto® Antihemophilic Factor (recombinant)

- **B-domain deleted recombinant factor VIII (BDDrFVIII)**
- **Produced through a genetically engineered Chinese hamster ovary cell line (CHO)**
- **Designed to correspond to the smallest of the multiple active forms of FVIII found in plasma-derived concentrates**
- **Complexity and heterogeneity have been greatly reduced through the elimination of the B-domain, which is not essential for hemostatic function**

Full-Length Factor VIII and ReFacto



ReFacto Comparable to Full-Length FVIII

- **In vitro functional assessment**
  - vWF binding
  - Thrombin activation
  - Inactivation by activated Protein C
  - FXa generation co-factor activity
- **Detailed structural analysis**
  - Primary protein structure
  - Carbohydrate structure
  - Other post-translational modifications

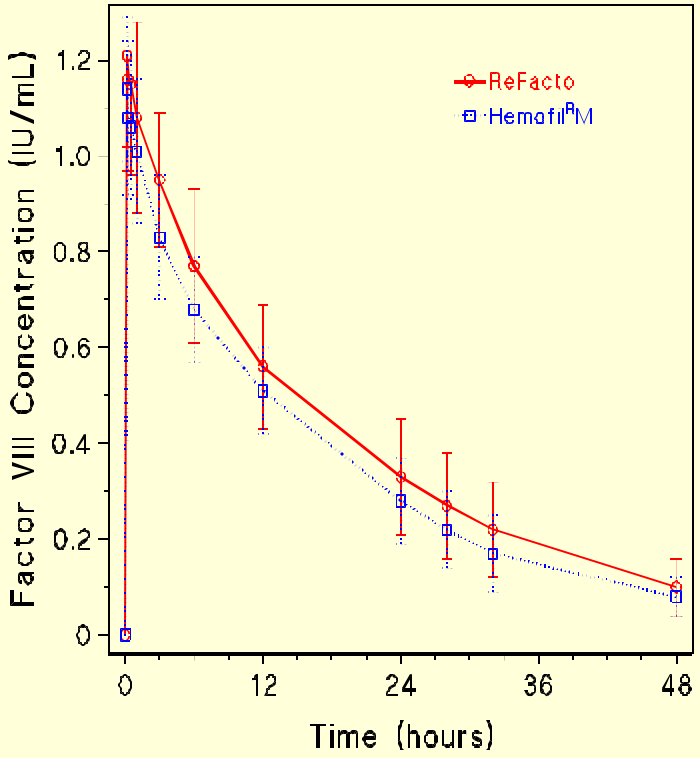
ReFacto Comparable to Full-Length FVIII

- **Pharmacodynamic studies in canine model of Hemophilia A demonstrate comparability**
  - Secondary cuticle bleeding times were corrected
  - Prolonged whole blood clotting times were corrected
  - Hemostatic correction occurred at the same dose and schedule as full-length FVIII
- **Single and repeated dose toxicity studies demonstrate comparability**
  - In rat and monkey studies, the toxicity profile is similar to that observed for plasma-derived factor VIII

Extensive Clinical Development Program

- **PK comparability with pdFVIII**
- **Safety / efficacy for bleeding control and prevention**
  - PTPs
  - PUPs
  - Surgery
  - Routine prophylaxis
  - On-demand
- **Clinical trials demonstrate ReFacto to be safe and effective**

ReFacto Bioequivalent to FL-pdFVIII



PK Parameters	ReFacto	pdAHF
Elimination half-life (hrs)*	14.5 ± 5.3	13.7 ± 3.4
FVIII activity increase IU/dL per IU/kg*†	2.4 ± 0.4	2.3 ± 0.3
In vivo recovery (%)*	118 ± 17	111 ± 14

** Mean ± S.D.*

†FVIII activity determined by chromogenic assay

ReFacto Study Design: PUP & PTP Trials

	PUP	PTP
Study Objective	Demonstrate long-term safety & efficacy of prophylaxis / on-demand	
Design	Open-label, non-comparative	
Treatment Plan	Prophylaxis, on-demand, follow-up to 6 years	
Key Eligibility	• Severe Hemophilia A (< 2% FVIII:C) • No history of transfusions with blood products	• Severe Hemophilia A (< 2% FVIII:C), age ³ 7 years • >1 year of prophylaxis treatment with FVIII or at least 30 ED / year • Absence of past or present inhibitors (³ 0.6 BU)
Demo-graphics	• 101 patients • Median age: 8 mos (range 0-52)	• 113 patients • Median age: 26 years (range 8-73)

ReFacto Efficacy

- **ReFacto efficacy was demonstrated in PUPs and PTPs**
- **Duration of treatment**

	Years on Study	Percent of Patients
PTPs	4 years	76%
	5 years	64%
	6 years	39%
PUPs	4 years	54%
	5 years	29%
	6 years	5%

- **Median ED**
  - **PTPs** 313 ED
  - **PUPs** 197 ED

ReFacto On-Demand Efficacy

	PUP	***PTP***
Episodes resolved with 1-2 infusions:	**85%***	**88%**
Excellent/Good Ratings:	**92%***	**92%**

* Bleeding episodes in PUPs who were inhibitor-free or until inhibitor detected

ReFacto Prophylaxis Efficacy

Prophylactic dosing reduces the rate of bleeding episodes

	No. bleeding episodes / year	
	On-Demand Periods	**Prophylaxis Periods**
PUPs		
No. patients	**45**	**45**
Mean ± SD	**11.4 ± 6.0**	**6.3 ± 5.2**
Median (*range*)	**10.0 (*2 - 28*)**	**5.0 (*0 – 22*)**
PTPs		
No. patients	**78**	**85***
Mean ± SD	**24.5 ± 24.6**	**10.3 ± 9.8**
Median (*range*)	**20 (*0 – 135*)**	**7 (*0 – 42*)**

* Seven (7) patients received prophylactic treatment for their entire time on study.

Factor VIII Inhibitor Testing During Clinical Trials

- **Extensive inhibitor monitoring**
- **Classic Bethesda Inhibitor Assay (BIA)**
  - Method precision: within 11%
  - Limit of Quantitation: 0.6 BU/ml
  - “No inhibitor” < 0.6 BU/ml
- **Three (3) independent BIAs performed centrally**
  - Normal human plasma test base
  - ReFacto test base
  - Nijmegen inhibitor assay

FVIII Inhibitors: ReFacto Clinical Trial Experience Similar to Full-Length FVIII for PUPs and PTPs

PUPs

- 32% (32 out of 101) of patients developed inhibitors
  - 16 were low-titer (<5 BU)
  - 16 were high-titer (≥5 BU)
- Consistent with other clinical trials with other rFVIII products
- Number of exposure days prior to inhibitor development
  - Median = 12 EDs (range 3 to 49)
- Inhibitor resolved (0 BU) in 25 of 32 patients (78%)
  - 20 of 25 patients who received ITT (Immune Tolerance Therapy)
  - 5 of 7 patients who did not receive ITT

PTPs

- 1 of 113 (0.9%) patients developed an inhibitor
  - Low-titer inhibitor of 1.2 BU at 98 ED
  - After 18 months, titer increased to 13 BU

Similar Inhibitor Rates in PTP Clinical Trials

- **Schwartz et al., *NEJM* 1990 (1st generation FL rFVIII)**
  - **High-titer *de novo* inhibitors developed in 2 of 86 PTP patients (2.3%; CI=0.28- 8.15)***
    - **In one of these patients, Western blot analysis of baseline samples detected antibody to factor VIII**
- **White et al., *Thromb Haemost* 1997 (1st generation FL rFVIII)**
  - **Inhibitors developed in 2 of 69 PTP patients (2.9%; CI=0.35-10.08)***
    - **1 patient with a remote history of a previous low-titer inhibitor**
    - **1 patient with a low-titer inhibitor at baseline that became a high-titer inhibitor**
- **Abshire et al., *Thromb Haemost* 2000 (2nd generation FL rFVIII)**
  - **Inhibitor developed in 1 of 71 PTP patients (1.4%; CI=0.04-7.60)***
    - **This patient had a low-titer inhibitor (0.39 BU) prior to study entry, considered *anamnestic***
- **Courter and Bedrosian, *Seminars in Hematology* 2001 (2nd generation BDD rFVIII)**
  - **1 in 113 PTP patients (0.9%; CI=0.02- 4.83) developed an inhibitor**

* Based on Wyeth analysis of article

Similar Inhibitor Rates in PTP Post-Marketing Observational Studies

- **McMillan et al., *Blood* 1988 (pdFVIII)**
  - **3.2% of patients developed inhibitors (n=919)**
  - **26 with ≥25 EDs**
  - **14 PTP (1.6%) with high-titer inhibitors (> 5 BU)**
- **Giles et al., *Transf Sci* 1998 (large Canadian experience in PTPs)**
  - **PTP patients switching from plasma-derived factor VIII to recombinant factor FVIII**
  - **1.9% of patients developed inhibitors at 1 year (n=478)**
  - **3.0% of patients developed inhibitors at 2 years (n=339)**
- **NHF (MASAC) 2003 (survey on high-titer inhibitors in PTPs)**
  - **45 centers responded (approximately 3500 patients)**
  - **12 PTPs (0.35%) with >50 EDs developed high-titer inhibitors in last 3 years**
    - **10 recombinant; 2 plasma derived product**
  - **6 of 12 inhibitor patients had more than 250 EDs**

Conclusions from Literature Review

- **Reported range for inhibitor development in PTPs: 0.9-3.2%**
- **Reported range for high titer inhibitors: 0-2.3%**
- **Broad and overlapping confidence intervals exists**
- **Definitions for inhibitors vary among reports**
  - **High vs. low-titer**
  - ***De novo* vs. anamnestic**
- **Need for a consistent standard for reporting inhibitors**

Wyeth Post-Marketing Inhibitor Surveillance

- **Wyeth reports *any* spontaneous event of inhibitor development with or without supportive clinical or laboratory data**
  - Extensive follow-up data collection
    - **Inhibitor specific questionnaire sent to all reporters**
    - **Follow-up telephone calls**
- **Wyeth definitions for post-marketing inhibitor reports**
  - No central laboratory testing performed
  - Positive titer: ≥ 0.6 BU
  - High-titer: ≥ 5.0 BU
  - Positive history of inhibitor: any previous titer ≥ 0.6 BU
  - *De novo*: no prior history of inhibitor ≥ 0.6 BU

Post-Marketing Experience with ReFacto*

- **Estimated 5800 patients treated worldwide**
  - **1450 PUPs**
  - **4350 PTPs**
- **83 reports of inhibitors**
  - **31 PUPs**
  - **24 classified as:**
    - **12 unknown ED or < 50 ED to all FVIII products**
    - **7 history of inhibitor prior to ReFacto therapy**
    - **4 inadequate medical history information**
    - **1 no titer obtained**
- **Therefore, 28 *de novo* inhibitors in PTPs with >50 ED to all FVIII products**
  - **20 low-titer (0.5%)**
  - **8 high-titer (0.2%)**

* Through April 2003

Initiatives in PTP Inhibitor Monitoring

- **Data in PTPs reporting inhibitors has led to a broad discussion**
  - Canadian prospective inhibitor surveillance
    - 3% incidence at two years
  - Review of UK inhibitor database
    - No product specificity
  - MASAC survey
    - High-titer inhibitors seen with pdFVIII and rFVIII
  - ISTH – interest in global surveillance program

Conclusions/Recommendations

- **Clinical trials, literature, and registries support:**
  - rFVIII and pdFVIII products have similar incidence of inhibitors
  - rFVIII and pdFVIII products have low incidence of high-titer inhibitors in PTPs
- **Global prospective surveillance needed to assess incidence of inhibitor development**
  - Defined period of patient observation
  - Standardized data collection techniques and definitions
  - Gathering of complete patient information including serial inhibitor testing, genotyping and other relevant data
- **Standardized spontaneous data collection leading to data-driven labeling**